

ACTIVE SENSOR AND METHOD FOR OPTICAL ILLUMINATION AND DETECTION**BACKGROUND OF THE INVENTION**

5

1. Field of the Invention

The present invention relates generally to optical measurement systems, and more specifically, to an active sensor illumination and detection apparatus for performing sample measurements using associated detector/illuminator groups integrated on one or more substrates.

2. Background of the Invention

15 One-dimensional and two dimensional measurement and inspection of samples is commonly performed in many industries, including biotechnology, semiconductor, micro electro-mechanical systems (MEMS) and others. For example, in the biotechnology industry, fluorescence measurements are used to determine the response of biological matter to illumination, thus revealing information about the composition and structure of a sample. Typically, for biological fluorescence tests, a sample or a material that is introduced to a sample is "tagged" with a fluorescent compound, the sample is illuminated with a laser, 25 and the resulting fluorescent emissions are mapped to determine

the locations of the fluorescent compound after interaction with the sample. For example, a prospective cancer drug may be tagged with a fluorescent compound and introduced to a sample having cancerous tissue. Then the sample is washed to remove excess
5 fluorescent compound. The sample is illuminated and resulting fluorescent emissions are mapped to determine whether or not the prospective drug has bound to the cancer active sensor cells.

The above-described process is typically performed on a bio
10 array, which may be a sample of DNA, gene chips including multiple DNA strands, microtiter plates with wells filled with various biocompounds, or microfluidic lab-on-a-chip devices. In each case, the device or sample is illuminated, typically by a scanning laser or filtered light source. Then, the resulting
15 fluorescence (or lack thereof) is mapped. The mapping is typically performed by either a scanning confocal microscope (SCM) or by imaging onto a charge-coupled-device (CCD) sensor.

The disadvantages of the above-described systems and
20 methods are long scanning times and moving parts for the SCM-based approach and lack of sensitivity and poorer spatial resolution for the CCD-based approach. A third alternative has been implemented, using a scanning laser and a photomultiplier tube for detection, but the cost of the scanning laser and

detectors is a disadvantage, as well as the requirement of a moving mechanism.

In another application, in the inspection of color quality
5 in materials, for example dye color, the sample may be
illuminated and the sample's optical behavior measured to
determine the properties of the sample. Measurement may be made
of reflectivity, absorption, transmission, secondary emission or
other optical property in order to determine sample
10 characteristics. In order to measure a sufficient field of view,
precise control over the color and angular spectrum must be
maintained for both illumination and detection systems. The
above requirements necessarily add tremendous complexity to any
measurement tool.

15

In the field of MEMS and semiconductor manufacture,
repetitive patterns are inspected for defects or anomalies. The
device under inspection is illuminated and scattered and/or
reflected light is imaged to determine properties of the device
20 under inspection. Such illumination and detection techniques
can be quite complex in order to provide the necessary
sensitivity and resolution.

Therefore, it is desirable to provide an alternative method and system for providing active illumination and detection for one-dimensional and two-dimensional inspection of samples having low cost, sufficient resolution, high sensitivity and high scanning speed for a broad range of applications.

5

SUMMARY OF THE INVENTION

The above objectives of providing a method and system for performing active one-dimensional and two-dimensional optical measurements having high speed, high sensitivity and low cost is accomplished in a method and apparatus. The apparatus comprises an active sensor including multiple illumination sources integrated to form a multi-pixel matrix. The matrix may have multiple rows and columns or may include just one row.

10

Multiple detectors are also integrated within illumination source matrix, each for detecting optical behavior of a sample resulting from the illumination of the sample by one or more of the illumination sources. One detector may be associated with multiple illuminators or one illuminator may be associated with multiple detectors. Filters may be integrated within the illumination and/or detection paths for providing wavelength and/or polarization discrimination capability and lenses may also be integrated within the illumination and/or detection paths providing variable working distances. A lens may be shared between one or more detectors and one or more illumination sources.

15

20

The foregoing and other objectives, features, and advantages of the invention will be apparent from the following, more particular, description of the preferred embodiment of the invention, as illustrated in the accompanying drawings, wherein
5 like reference designators indicate like elements.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a pictorial diagram depicting an active sensor system including an apparatus in accordance with an embodiment
5 of the present invention.

Figure 2A is a pictorial diagram depicting details of an active sensor in accordance with an embodiment of the present invention.

Figure 2B is a pictorial diagram depicting details of an
10 active sensor in accordance with another embodiment of the present invention.

Figure 2C is a pictorial diagram depicting details of an active sensor in accordance with yet another embodiment of the present invention.

Figure 2D is a pictorial diagram depicting details of an
15 active sensor in accordance with still another embodiment of the present invention.

Figure 3 is a pictorial diagram depicting details of an active sensor in accordance another embodiment of the present
20 invention.

Figure 4 is a pictorial diagram depicting details of an active sensor system in accordance another embodiment of the present invention.

DETAILED DESCRIPTION OF THE EMBODIMENTS

While the below description is limited, by the way of example, to the measurement of a fluorescent sample, it is understood that the function will be similar for samples such as colored materials, MEMS or semiconductor devices, and/or repetitive patterns, and other applications. In order to avoid repetition, it is understood that the same description will be applicable to other applications that measure optical properties of samples.

Referring now to the figures and in particular to **Figure 1**, a system including an active sensor **10** in accordance with an embodiment of the present invention is shown. Active sensor **10**, which includes a plurality of active sensor active sensor cells **11**, is placed in close proximity with a sample frame **12**, that may contain samples of biological matter tagged with a fluorescent material, or other samples under inspection such as a semiconductor device, for which a standard handling frame may be employed. Active sensor cells **11** each include one or more detectors and one or more illumination elements integrated on the substrate. While the depiction shows a two-dimensional active sensor **10**, active sensor **10** may also be a one-dimensional

active sensor, comprising only one row of active sensor cells
11.

The detection elements within active sensor cells **11** are coupled to a processing subsystem for detecting light scattered
5 or emitted from associated portions of the samples. The association is by virtue of the proximity of the active sensor cells **11** to the sample frame **12** so that the fields of the detectors generally do not substantially overlap, or so that any overlap is generally limited to adjacent pixels. Similarly, the
10 illumination element fields also do not substantially overlap in general and can be used to selectively illuminate portions of the samples. Sample frame **12** may comprise a plurality of wells, as in a microtiter plate or other multi-sample/multi-cell device, in which case, the spacing and location of active sensor
15 cells **11** can be dictated by the spacing and location of wells in sample frame **12**. One cell **11** may correspond to a single well, giving active sensor **10** the ability to simultaneously process optical information at each cell without requiring a scanning mechanism.

20

Alternatively, sample frame **12** may comprise a single contiguous sample, such as a tissue sample or single sample having multiple discrete portions such as a DNA gel. Where discrete boundaries are not present, it may be desirable to

sequentially illuminate the illumination elements individually, or program an illumination pattern such that adjacent illumination elements do not cause illumination of portions of a sample associated with other illumination elements. Illumination control subsystem **16** provides for control of illumination elements within active sensor cells **11** and is coupled to a processing subsystem **14** that receives the outputs of detectors within active sensor cells **11**. The interconnection of illumination control subsystem **16** with processing subsystem **14** permits synchronization of illumination and detection permitting accurate determination of response time and correlation of detected fluorescent emissions to the activation of an illumination element within a cell **11**. In addition, illumination elements can be pulsed or modulated and detection elements can be shuttered or time-gated to allow complex temporally resolved measurement schemes.

In other embodiments of the present invention, sample frame **12** may hold samples comprising a matrix of colored elements or samples may have a scattering pattern such as found on MEMS or semiconductor devices. The function of the system is identical to that described previously except that the detected light is no longer fluorescent emission, but scattered light.

The illumination elements included within active sensor cells **11** are substrate-integrated sources that may be provided by TFT-LCD devices, diode emitters, organic LEDs (OLEDs), vertical cavity emitting lasers (VCELs) or other light sources that may be integrated to form a high-density illumination matrix. The detectors included within active sensor cells **11** may be PIN photo-diodes, CCD sensors, CMOS sensors or other detectors that are suitable for integration within the illumination matrix. Lenses are optionally included for coupling a cell or field of active sensor cells **11** to samples or portions thereof and may be implemented using standard microlenses, graded-refractive-index (GRIN) lenses, fiber couplers or other suitable focusing/coupling or imaging mechanism.

Referring now to **Figure 2A**, details of an active sensor **10A** including active sensor cells **11A**, in accordance with an embodiment of the present invention are shown. **Figure 2A** also shows an exemplary sample frame **12A** including sample elements **20** (depicted as wells in a microtiter plate) that are associated with particular active sensor cells **11A** via proximity of sample frame **12A** to active sensor **10A**. A substrate **28A** supports active sensor cells **11A** and a cover glass **22** is optionally included to protect active sensor cells **11A** and may be spaced above active

sensor cells **11A** as shown, or placed in contact with active sensor cells **11A**.

The structure of active sensor cells **11A** is shown in
5 balloon **23A**. A single illumination element **24A** is paired
(associated) with a single detector **27A** for detecting
fluorescence of biological matter deposited in an associated
sample element **20A** due to illumination from illumination element
24A (or other optical characteristics in non-fluorescence
10 measurements). A microlens **25A** is optionally integrated over
illumination element **24A** and detector **27A** for focusing or
imaging a field of illumination element **24A** and detector **27A** on
or within sample element **20A**. A filter **26A** is integrated between
detector **27A** and microlens **25A** for providing a passband response
15 around a specific optical wavelength and/or a polarization
characteristic, providing wavelength and/or polarization
selectivity in the output response of detector **27A**, whereby a
specific fluorescence band is detected by detector **27A**.
Illumination element **24A** is generally a narrowband emitter in
20 the present configuration, but in some applications may be a
broadband source, depending on whether or not the measurement
being made is dependent on a specific excitation wavelength. The
embodiment depicted in **Figure 2A**, is exemplary of a single-
detector, single-illumination element pairing that is associated

with a unique portion of a sample or unique samples of a sample frame by virtue of the sample proximity. Other configurations depicted in other embodiments below or otherwise understood to be encompassed by the present invention include other groupings of multiple or single detectors to multiple or single illumination elements or arrangements including a multi-pixel illumination element array interspersed with a multi-pixel detector array where no specific grouping of detectors and illumination elements is employed. Similarly, it is understood that various geometric arrangements of the illumination/detector pair can be used, including side-by-side, concentric arrangements, quad detectors and others and that an imaging system may be used so that the array or arrays do not have to be placed in close proximity to the samples.

Referring now to **Figure 2B**, details of an active sensor **10B** including active sensor cells **11B**, in accordance with another embodiment of the present invention are shown. **Figure 2B** also shows an exemplary sample frame **12A** including sample elements that are associated with particular active sensor cells **11B** via proximity of sample frame **12A** to active sensor **10B**. A substrate **28B** supports active sensor cells **11B** and cover glass **22** is optionally included to protect active sensor cells **11B** and may

be spaced above active sensor cells **11B** as shown, or placed in contact with active sensor cells **11B**.

The structure of active sensor cells **11B** is shown in
5 balloon **23B**. A single illumination element **24B** is paired
(associated) with a single detector **27B** for detecting
fluorescence of biological matter deposited in an associated
cell forming sample element **20A** due to illumination from
illumination element **24B** (or measuring other optical
10 characteristics in non-fluorescence measurements). A microlens
25B is optionally integrated over illumination over illumination
element **24B** and detector **27B** for focusing or imaging a field of
illumination element **24B** and detector **27B** on or within well **20A**.
A filter **29B** is integrated between illumination element **24B** and
15 microlens **25B** for providing a passband response around a
specific optical wavelength and/or polarization characteristic,
providing a narrowband and/or polarization-controlled
illumination source. Illumination element **24B** is generally a
broadband emitter in the present configuration.

20

Another filter **26B** is integrated between detector **27B** and
microlens **25B** for providing a passband response around a
specific optical wavelength and/or a polarization
characteristic, providing wavelength and/or polarization

selectivity in the output response of detector **27B**, whereby a specific fluorescence band is detected by detector **27B**. Filters **26B** and **29B** are not constrained to have the same passband wavelength, as the fluorescent response of a material may differ greatly from the specific excitation wavelength used to excite the biological sample. The embodiment of cell **11B** depicted in **Figure 2B** is another example of a single-detector single-illumination element pairing. Other possible combinations include a filtered illumination source with an unfiltered detector, polarized illumination source with filtered detector and other combinations of passband and/or polarizer filters.

Referring now to **Figure 2C**, details of an active sensor **10C** including active sensor cells **11C**, in accordance with yet another embodiment of the present invention are shown. **Figure 2C** also shows an exemplary sample frame **12A** including sample elements (wells) **20** that are associated with particular active sensor cells **11C** via proximity of sample frame **12A** to active sensor **10C**. A substrate **28C** supports active sensor cells **11C** and cover glass **22** is optionally included to protect active sensor cells **11C** and may be spaced above active sensor cells **11C** as shown, or placed in contact with active sensor cells **11C**.

The structure of active sensor cells **11C** is shown in balloon **23C**. Multiple illumination elements **24C** are paired (associated) with a single detector **27C** for detecting fluorescence of biological matter deposited in an associated sample element **20A** due to illumination from illumination elements **24C** (or other optical characteristics in non-fluorescence measurements). A microlens **25C** is optionally integrated over illumination over illumination elements **24C** and detector **27C** for focusing or imaging a field of illumination elements **24C** and detector **27C** on or within well **20A**. A filter **26C** is integrated between detector **27C** and microlens **25C** for providing passband response around a specific optical wavelength and/or a polarization characteristic, providing wavelength and/or polarization selectivity in the output response.

Illumination elements **24C** are generally narrowband emitters having separate predetermined illumination wavelengths in the present configuration and are generally controlled by illumination control subsystem **16** so that fluorescent response of samples or portions thereof to multiple predetermined wavelength excitation can be determined by enabling first one set of illumination elements in active sensor cells **11C** corresponding to a first wavelength and then a second set of illumination elements in active sensor cells **11C** corresponding to a second wavelength and observing the response using

detectors **27C**. The embodiment depicted in **Figure 2C** is an example of multiple-illumination element, single-detector grouping. The number of associated illumination elements to a single detector also may be greater than two.

5

Referring now to **Figure 2D**, details of an active sensor **10D** including active sensor cells **11D**, in accordance with still another embodiment of the present invention are shown. **Figure 2D** also shows an exemplary sample frame **12A** including sample
10 elements (wells) **20** that are associated with particular active sensor cells **11D** via proximity of sample frame **12A** to active sensor **10D**. A substrate **28D** supports active sensor cells **11D** and cover glass **22** is optionally included to protect active sensor cells **11D** and may be spaced above active sensor cells **11D** as
15 shown, or placed in contact with active sensor cells **11D**.

The structure of active sensor cells **11D** is shown in balloon **23D**. Multiple detectors **27D** are paired (associated) with a single illumination element **24D** for detecting fluorescence of
20 biological matter deposited in an associated sample element **20A** due to illumination from illumination element **24D** (or other optical characteristics in non-fluorescence measurements). A microlens **25D** is optionally integrated over illumination element **24D** and detectors **27D** for focusing or imaging a field of

illumination element **24D** and detectors **27D** on or within well
20A. Multiple filters **29D** are integrated between detectors **27D**
and microlens **25D** for providing a unique passband response
around a specific optical wavelength for each detector **27D** in a
5 cell **11D**, providing multiple narrowband detector responses.
Alternatively or in combination, filters **29D** may provide
multiple polarization responses, providing the ability to
determine polarization ratios, and so forth. Illumination
element **24D** is generally a narrowband emitter for exciting a
10 sample or portions thereof and detectors **27D** in conjunction with
filters **29D** provide separate responses to the illumination,
whereby multiple fluorescence band emissions can be
simultaneously detected in response to narrowband excitation.
The embodiment depicted in **Figure 2D** is an example of single-
15 illumination element, multiple-detector grouping. The number of
associated detectors to a single illumination element also may
be greater than two.

Referring now to **Figure 3**, details of an active sensor
20 system in accordance with an embodiment of the present invention
are shown. Two separate array devices are employed, device **10E**
is a detection array that includes elements as depicted in
balloon **23E**, including detectors **27E** filters **26E** and microlens
25E. Device **10F** is an illumination array including illumination

elements **24F** and microlenses **25F** as depicted in balloon **23F**.

However, the elements may be variations on the depicted structure in accordance with the above-described element types and either or both arrays may include both illumination and
5 detection elements. For example to provide a transmission and reflection/scattering measurement, device **10F** may also include detection elements for detecting back-scattered light associated with each illumination element and/or sample element **20E**.

10 The system of **Figure 3** is particularly suited for transmission measurements as detector device **10E** is on the opposite side of samples **20E** from illumination device **10F**. Groups associating detectors **27E** and illumination elements **24F** in the system of **Figure 3** are associated by the location the
15 fields of light transmitted by particular illumination elements **24F** and received by particular detectors **27E**, rather than also being associated by proximity as in the other exemplary embodiments described above, and as such, comprise the active sensor "cells" in the present embodiment. Both device **10E** and
20 device **10F** are fabricated on substrates (**28E** and **28F** respectively) and may include cover glasses (**22E** and **22F** respectively). It should be noted in all of the above examples, filtering may be provided by a "gel" or colored cover glass that is provided in addition to or in place of the illustrated cover

glasses for providing a wavelength/or polarization filtered optical characteristic within the system.

Referring now to **Figure 4**, an active sensor system in accordance with yet another embodiment of the present invention is depicted. Active sensor **10G**, which may be any of the active sensors described above or variations thereon, is coupled by an imaging lens **41** to sample elements **20G**. The imaging system may alternatively be or include optical fibers, waveguides of other type or any known method for "remoting" (or "relaying") an image from sample elements **20G** to active sensor **10G**. As long as a grouping via the image is made between illumination elements and detection elements within active sensor **10G**, detection of individual sample element **20G** behavior is provided. Optical paths (such as optical paths **42** and **43**) associate co-located detection and illumination elements within active sensor **10G** with a particular sample element (e.g., optical path **42** associates a particular detector/illuminator with sample element **20G**). Alternatively, separate detection and illumination devices may be provided and coupled via beam-splitters, couplers or physical arrangement (angular orientation, etc.), so that an association between one or more detection elements and one or more illumination elements is preserved. While the embodiment shown uses a single lens **41** to relay light between active sensor

10G element groups and sample elements with an inverted position relationship, other lens/relaying-device configurations may be employed including position-rectified configurations.

5 While the invention has been particularly shown and described with reference to the preferred embodiments thereof, it will be understood by those skilled in the art that the foregoing and other changes in form, and details may be made therein without departing from the spirit and scope of the
10 invention.